The epidemiology of hyperprolactinaemia over 20 years in the Tayside region of Scotland

Soto-Pedre, Enrique; Newey, Paul J.; Bevan, John S.; Greig, Neil; Leese, Graham P.

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TITLE PAGE

Title: The epidemiology of hyperprolactinaemia over 20 years in the Tayside region of Scotland: The Prolactin Epidemiology, Audit, and Research Study (PROLEARS)

Short title: Epidemiology of hyperprolactinaemia.

Authors: Enrique Soto-Pedre [1], Paul J. Newey [1, 2], John S. Bevan [3], Neil Greig [4], Graham P. Leese [2]

Authors' affiliations:

[1] Division of Molecular & Clinical Medicine, School of Medicine, Ninewells Hospital and Medical School, University of Dundee (Dundee, UK)

[2] Department of Endocrinology and Diabetes, Ninewells Hospital and Medical School, University of Dundee (Dundee, UK)

[3] JJR Macleod Centre for Diabetes, Endocrinology & Metabolism (Mac-DEM), Aberdeen Royal Infirmary, University of Aberdeen (Aberdeen, UK)

[4] Department of Clinical Biochemistry, Ninewells Hospital and Medical School, University of Dundee (Dundee, UK)

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Corresponding author and person to who reprint requests should be addressed:

Enrique Soto-Pedre MBBS, MSc

Division of Molecular & Clinical Medicine, School of Medicine

Level 5, Mailbox 12

Ninewells Hospital and Medical School, University of Dundee

Dundee DD1 9SY, Scotland (UK)

Phone: +44(0)1382383585 Fax: +44(0)1382383598 E-mail: e.soto@dundee.ac.uk

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ABSTRACT

Objective: To estimate the prevalence and incidence of hyperprolactinaemia. Hyperprolactinaemia is a common problem in endocrine practice, but its epidemiology has not been accurately established.

Study design: A population-based retrospective follow up study in Tayside, Scotland (population 400,000) from 1993 to 2013.

Patients: Record-linkage technology (biochemistry, prescribing, hospital admissions, radiology, mortality and maternity data) was used to identify all patients with a serum

prolactin measurement. From these, cases were defined as those with a prolactin greater than 1000mU/L (47.2ng/ml) or at least three prescriptions for a dopamine agonist.

Measurements: Number of prevalent and incident cases of hyperprolactinaemia per calendar year by age, sex and cause of hyperprolactinaemia.

Results: A total of 32,289 patients had a serum prolactin assay undertaken, of which 1,301 had hyperprolactinaemia not related to pregnancy: 25.6% patients were pituitary-disorder 45.9% drug-induced, 7.5% related to macroprolactin, and 6.1% related to hypothyroidism, leaving 15.0% idiopathic. Over the 20 years there was a fourfold increase in the number of prolactin assays performed and prevalence of hyperprolactinaemia was initially 0.02%, but rose to 0.23% by 2013. Overall incidence was 13.8 cases per 100,000 person-years (20.6 in 2008-13) and was 3.5 times higher in women than in men. The highest rates were found in women aged 25-44 years. Drug-induced causes tripled during the 20 years.

Conclusions: Rising prevalence of hyperprolactinaemia is probably due to increased ascertainment and increased incidence of psychoactive drug-related causes. Rates are higher in women than in men but only before the age of 65 years.

INTRODUCTION

Prolactin is a pleiotropic hormone with defined effects on lactation and gonadal function, whilst also influencing numerous additional physiological processes encompassing metabolism, angiogenesis, neuronal function, osmoregulation and immunity [1, 2]. Hyperprolactinaemia, an excess of serum prolactin above a laboratory reference limit, is a common problem in endocrine practice [3, 4].

Hyperprolactinaemia can be physiological, pathological or iatrogenic. The causes of persistent non-physiological hyperprolactinaemia (i.e. occurring outside of gestation or lactation) include drugs, hypothyroidism, and hypothalamic/pituitary disorders [5]. The association with certain drugs is well documented, most commonly antipsychotic agents [6, 7]. Other medications include antidepressants, anti-emetics and antihypertensive agents [8]. Macroprolactin resulting from the formation of prolactin-immunoglobulin complexes is associated with apparent hyperprolactinemia, although not typically associated with clinical features due to limited bioavailability and bioactivity. Aside from these, idiopathic hyperprolactinaemia is not uncommon [3]. Data from case series and cross-sectional studies in patients with hyperprolactinaemia suggest that prolactinomas and other pituitary tumour types (35-70%) and idiopathic hyperprolactinaemia (28-46%) are the most common categories [9-14], but the majority of studies excluded drug-induced cases. The large number of commonly prescribed medications associated with hyperprolactinaemia suggests it is likely to occur frequently in the population, although its frequency has rarely been documented; Vilar et al reported a prevalence of 14.5% drug induced cases from a sample of patients identified at ten endocrine centres in Brazil [11]. Regardless of aetiology, hyperprolactinaemia may result in hypogonadism, infertility, amenorrhoea, galactorrhoea, and impotence or it may produce no symptoms [15].

Hyperprolactinaemia may occur in men and women at any age, and its prevalence and incidence depends on the study population. Its epidemiology in the general population has not been accurately established, because available estimates are scarce and/or inadequate. Prevalence from cross-sectional studies seems to vary from 1.2-4.1% in healthy adults [16, 17] to 3.9-30% in series of patients identified in various clinical settings; it was estimated at 3.9% in patients identified through a private large medical centre database, 7.9% among women

with menstruation related problems, 15.7% among women attending to an infertility clinic, 18% in patients with systemic lupus erythematosus, and 30% among women receiving oral contraceptives [18-22]. The prevalence was 3.1% among male patients with idiopathic sexual dysfunction [23]. However results from a population-based cohort study showed a much lower overall prevalence of "ever" medically treated hyperprolactinemia that ranged from 0.02% in men to 0.09% in women, and incidence ranged from 1.4/100,000 person-years in men to 8.7/100,000 person-years in women [24]. The prevalence of pituitary tumours have been shown to be around 1 per 1000 of the population [25, 26], with 44% being due to prolactinomas in one study [26]. However, population-based estimates of the incidence and prevalence of all causes of hyperprolactinaemia are still lacking.

The Centre for Endocrine Epidemiology in Tayside (Scotland, UK) has undertaken data linkage to report on incidence and prevalence of thyroid dysfunction and primary hyperparathyroidism [27, 28]. We aimed to use the same data linkage to estimate prevalence and incidence of all cause hyperprolactinaemia in the general population as well as the relative contribution of the respective causes.

SUBJECTS AND METHODS

Anonymised data from medical records of patients for the complete population of Tayside, a well-defined geographical region within Scotland (UK) with a population of 400,000 people, were reviewed between 1988 and 2014 (the most recent data available). Every patient in Tayside has a unique National Health Service (NHS) patient identifier (Community Health Index- CHI) number that has been used for all health related contacts, whether in primary, secondary or private health care. This allowed the electronic linkage of all databases used.

The Biochemistry database was linked to other databases by the Health Informatics Centre Services/ Farr Institute of Scotland at the University of Dundee (http://www.dundee.ac.uk/hic). These included demographic records (gender, birth and migration), Scottish Morbidity Records-SMR (maternity admissions, hospital admissions, and surgical procedures), Scottish Care Information-Diabetes Collaboration-SCI-DC database (data from primary care and diabetes clinics on diabetes mellitus), prescriptions dispensed, and the General Registrar Office-GRO records on patient deaths. Magnetic Resonance Imaging (MRI) reports were also accessed and linked for identifying pituitary tumours [29].

Prolactin analyses were performed using three analytical platforms during the period of the study. Up to 2003 levels were measured by a Bayer® chemiluminescence immunoassay (Bayer PLC, Newbury, UK), from 2003 to 2012 by a Roche® E170 electrochemiluminescence analyser (Roche Diagnostics Limited, West Sussex, UK), and since then by a Siemens ADVIA Centaur XP® chemiluminescence analyser (Siemens Healthcare Diagnostics, Surrey, UK). The reference range for prolactin was less than 600mU/L (28.3ng/ml) for women and less than 350mU/L (16.5ng/ml) for men, and did not change over time. All analyses had been performed at the Blood Sciences Department at the Ninewells Hospital (Dundee, UK).

The International Classification of Diseases (ICD) 10th revision codes were used to identify hospital inpatient events, and the Office of Population Censuses and Surveys Classification of Surgical Operations version 4 codes (OPCS-4) to identify operations, procedures and interventions during inpatient stays. Prescriptions were identified by means of the British National Formulary (BNF) codes.

To ensure data quality, SMR data go through a set of validation rules by the Information Services Division (ISD-NHS National Services Scotland). These validation rules check on the validity and feasibility of the data [30]. Besides, ISD carry out periodical data quality assurance exercises to evaluate and ensure SMR datasets are accurate, consistent and comparable across time and between sources [31]. The study was approved by the Tayside Committee for Medical Research Ethics and conducted in accordance with the Declaration of Helsinki.

Inclusion-exclusion criteria and case definition

Patients with at least one serum prolactin measurement taken were considered for inclusion in the study. All patients who were pregnant or possibly lactating at the time of assay (i.e. within 9 months before and 12 months after delivery date) were excluded, unless they had raised prolactin measurements out with this time window. Any patient with at least one serum prolactin measurement greater than 1,000mU/L (47.2ng/ml) or three or more prescriptions of specific dopamine agonists (BNF 6.7.1: cabergoline, bromocriptine, and/or quinagolide) was considered a case, with subsequent allocation into one of five groups:

1. **Pituitary-disorder.** Patients were selected if they had at least one serum prolactin measurement greater than 5,000mU/L (235.8ng/ml), or three or more prescriptions of specific dopamine agonists and/or a hospital admissions related to pituitary disorder (ICD10: C751, E22, E23) and/or pituitary surgery (OPCS-4: B01, B02, B04) or a mass on pituitary MRI.

2. **Drug-induced**. Patients were selected if they had a record of being prescribed drug(s) known to elevate prolactin levels within 6 months before and 1 month after the assessment of serum prolactin measurement, and did not fit into group 1. Any prescription of antipsychotics (BNF: 4.2.1, 4.2.2), tricyclics and related

antidepressants (BNF: 4.3.1), serotonin re-uptake inhibitors (BNF: 4.3.3), dopamine antagonists (BNF: 4.6), opioids and drugs used in opioid dependence (BNF: 4.7.2, 4.10.3), H2 antagonists (BNF: 1.3.1), methyldopa (in BNF: 2.5.2), and verapamil (in BNF: 2.6.2) were extracted from the database containing prescriptions dispensed from all community pharmacies in Tayside.

3. **Macroprolactin**. Patients were selected if they had presence of macroprolactin identified without any other explanation.

4. **Hypothyroidism**. Patients were selected if they had a thyroid stimulating hormone (TSH) serum level > 6mU/L (0.28ng/ml) at some time without any other explanation.

5. **Idiopathic**. Patients were selected if remained unclassified.

Statistical analysis

The period of study for the analysis of prevalence and incidence was defined between January 1st 1993 and January 1st 2013 to avoid bias introduced by incomplete ascertainment of cases before and after these dates. Any patient with at least one serum prolactin measurement greater than 1,000mU/L (47.2ng/ml) or three or more prescriptions of specific dopamine agonists at any time within a year was considered a prevalent case. Period prevalence was then estimated as the number of prevalent cases divided by the estimated mid-year population originated from the GRO records for Scotland, and it was calculated for every calendar year and for the entire period of study. For each patient the date of entry into the study was the date at first event of diagnosis identified within this period, and it was assumed that a patient after diagnosis stayed prevalent for the rest of the study until death or moving out of the health area. The incidence rate was calculated as the number of new (i.e. incident) cases divided by the number of person-years in the source population. Person-

years were calculated for every calendar year separately and further combined for all calendar years to serve as the denominator of an overall incidence rate. Incidence rate was stratified by gender and 10-year age groups group (<15, 15-24, 25-34, 35-44, 45-54, 55-64, 65-74, 75+); 95% confidence intervals (CIs) for these were calculated assuming a Poisson distribution. Standardized rates were calculated by applying the age/sex-stratified rates to the all-Scotland population from the 2001 and 2011 (estimates for 2002 to 2013) Census results. Data were entered into a STATA/SE® version 13.1 software package (StataCorp, USA) for statistical analysis and determination of statistical significance (P values <0.05). Logic checks were performed and frequency distributions for all variables were analysed for out-of-range values. The mean and standard deviation or the median and the interquartile range of the data were calculated to describe continuous variables. ANOVA and chi-square tests were used to compare means and frequencies among subgroups of patients respectively. Nonparametric methods were used where appropriate[32].

RESULTS

A total of 32,289 patients were identified with at least one measurement of a serum prolactin level in Tayside between 1988 and 2014, 1,366 of whom met the criteria for hyperprolactinaemia. After excluding 65 cases of hyperprolactinaemia associated with pregnancy, a total 1,301 cases were considered for the study. Demographic characteristics of the final study cohort are shown in Table 1. The mean age was 39.2 years, and 78.3% were women. Of these cases, the majority were drug-induced (45.9%), followed by pituitary-disorder (25.4%). Drug-induced cases were older (mean age 42 years) and pituitary-disorder cases had the highest average of maximum serum prolactin concentration (2,426mU/l; 114.4ng/ml) at diagnosis compared to other causes (P<0.001). Anti-psychotic and anti-depressant medications accounted for 63.5% and 12.7% of drug-induced cases respectively,

and a total of 228 out of 598 drug-induced cases (38%) also had traces of macroprolactin. Of 331 patients categorised as having a pituitary disorder we identified MRI pituitary scans in 250 (76%). The remainder are likely to have had a scan outwith Tayside or at a time before the study entry. Out of pituitary caused cases found, 145 had confirmatory abnormalities on pituitary MRI, of which 91 (62.8%) were micro-adenomas, and 54 (37.2%) macro-adenomas. The respective data for micro-adenomas and macro-adenomas were: mean ages 35.9 and 48.5 years (P<0.0001), percentage female 83.5% and 55.6% (P<0.0001), median maximum serum prolactin concentration of 2,103mU/L (99.2ng/ml) and 3,618mU/L (170.7ng/ml) (P=0.039). In all other patients 111 underwent a pituitary MRI scan, all of which were normal. Overall 6.1% of cases patients had a TSH greater than 6mU/L (0.28ng/ml) and no other explanation for hyperprolactinaemia. No cause could be found for the hyperprolactinaemia in 196 cases (15%), although 17 of these had undergone MRI scanning with a normal result, and these cases may have represented a micro-prolactinoma.

Prevalence and incidence rates of ever treated and untreated (i.e. measured) hyperprolactinaemia were estimated for the period 1993-2013 for the population of Tayside that increased from 395,480 to 411,750 (table 2). There was also a steep increase in the number of serum prolactin assays carried out in Tayside around 2003, changing from 9,167 in 1998-2002 to 34,221 in 2003-2007 (Table 3). The overall prevalence of ever having had hyperprolactinaemia was 107.3 cases per 100,000 population, and it was five times higher in women (175.2 per 100,000) than in men (35.1 per 100,000). Prevalence increased continuously over the calendar years from 0.02% in 1993 to 0.23% in 2013 (table 2). The average year-on-year increase was 15.7% for women and 17.2% for men.

A total number of 1,102 incident cases were ascertained (862 women and 240 men). Crude incidence rates were about three times higher in women than in men, and were lower in periods earlier than 2003 (table 3). When crude incidence rates were adjusted for age and sex using GRO for Scotland Census results, the overall rate was 13.8 per 100,000 person-years (95%CI: 13.1- 14.7), with a rate of 21.5 per 100,000 person-years (95%CI: 20.0- 22.9) observed for women and 6.4 per 100,000 person-years (95%CI: 5.6- 7.2) for men.

Incidence rate of hyperprolactinaemia increased for men through the study period, and increased for women from 2003. The increased rate over the last year periods (2003 to 2013) was mostly due to an increase of drug-induced cases (table 4), but also due to an increased recognition of macroprolactin. There was also an increase of pituitary diagnoses for men in 2008- 2013 (table 4).

When rates were examined for combined periods by age and sex groups (figure 1), the highest incidence rates of hyperprolactinaemia were found in women aged 25-44 years (25-34 years: 49.6 per 100,000 person-years, 35-44 years: 42.7 per 100,000 person-years), and after this peak the incidence rates declined with age. In men, no peak was found, and the incidence rates ranged from 6 to 8.8 per 100,000 person-years in those people older than 15 years. When rates were examined also by cause of hyperprolactinaemia (figure 2), a similar trend was observed in women for pituitary disorder, drug-induced, macroprolactin, and hypothyroid-related cases. In men, drug-induced and hypothyroid-related rates followed the same trend, but rates of pituitary disorder hyperprolactinaemia increased in those diagnosed over the age of 55 years and were also higher than in women. Incidence rates of idiopathic hyperprolactinaemia showed a peak in men and women aged 25-34 years.

DISCUSSION

Over the last 20 years the prevalence of people having ever had hyperprolactinaemia increased from 22 to 232 per 100,000 in the 20 years following 1993, and steady state has not been achieved. The prevalence was approximately five times greater in women than in men. The adjusted incidence of all causes for hyperprolactinaemia was 13.8 per 100,000, increasing from 9 to 20 per 100,000 over 20 years. The incidence in women was 3.5 times that observed in men, but there was little gender difference above the age of 55 years.

There are a number of possible reasons for this increasing incidence and prevalence of hyperprolactinaemia. The number of prolactin tests performed across Tayside during the study period increased from 2,332 in 1993 to 8,688 per annum in 2012, with a steep increase in 2003 (5,306 prolactin tests). Increased number of tests would be expected to result in an increased ascertainment of cases of hyperprolactinaemia. There was an increased rate of drug-induced hyper-prolactinaemia, which is likely to reflect an increased use of anti-psychotic and anti-depressant medications over this time. Prolactin measurements are sometimes used as a marker of concordance in such patients. Routine testing for macroprolactin started around 2002 and such diagnoses increased steadily after 2003, as the prevalence of idiopathic causes declined. It is likely that many cases of idiopathic hyperprolactinaemia before 2002 were due to macroprolactin. The increase in pituitary-disorder diagnoses for men during the last period of study (2008- 2013) is intriguing and may reflect an increasing awareness of impotence and an increasing willingness to investigate it [33]. It is difficult to be certain if there was real increase in hyperprolactinaemia or whether changes simply reflect an increased ascertainment, along with some real increase in drug-induced cases. Either way, the increased incidence does indicate an increased demand on health-care resources.

As described previously, the prevalence of hyperprolactinaemia is reported to vary greatly from studies of healthy adults to series of patients identified in various clinical settings. Despite these variations, studies on community-based data reported prevalence of measured hyperprolactinaemia (women>600mU/L and men>400mU/L) between 1.2-1.4% [16] from a relatively small cohort of 1,675 people, but in a study where all patients were sampled. In another larger study the prevalence of hyperprolactinaemia, identified by use of more than one dopamine agonist prescription, was 0.03-0.17% [24]. The prevalence increased over the study period, due partly to an increasing incidence. Our results agree in part with those from the population-based cohort study of Kars et al. that showed a prevalence of ever medically treated hyperprolactinemia around 0.2% in recent years, and five times greater in women than in men [24]. However, Kars at al. did not present data either on death or migration of patients, excluded individuals aged less than 15 years, and did not include untreated hyperprolactinaemia in their case ascertainment.

Kars et al. reported an incidence rate of treated hyperprolactinaemia of 5.1 per 100,000 [24]. This mainly reflected pituitary tumours but possibly with some other cases of hyperprolactinaemia treated with dopamine agonists. Unlike the Kars study our report included pituitary imaging (MRI) information, and reported an incidence of pituitary tumours of around 4 per 100,000 since the year 2000. If several of our idiopathic group were due to micro-prolactinomas, then our figure would be very similar to that of Kars. The highest incidence rate was found in women aged 25-34 years, and after this peak rates remained high in those aged 35-44 years, and declined with age similar to the Kars study [24]. In men pituitary-disorder rates increased in those over the age of 55 years. This may reflect increasing investigation of impotence and low serum testosterone. The majority of pituitary caused cases (92.5%) were treated with dopamine agonists (three or more prescriptions),

but some milder cases remained untreated. In addition to the Kars study we report a drug induced rate of hyperprolactinaemia of 6.7 per 100,000 indicating that this is now the commonest cause of hyperprolactinaemia.

Defined cases in our study included patients with a serum prolactin greater than 1000mU/L (47.2ng/ml) and may thus have missed some cases of clinically-relevant hyperprolactinaemia with more modest prolactin elevations. This threshold of serum prolactin (rather than one defined according to gender specific reference ranges) was chosen because it represents a clinical relevant elevation of prolactin that deserves further investigation in practice, and thus additional health-care resources. This particularly diagnostic criterion may have contributed to underestimate untreated hyperprolactinaemia mainly in men, but it seems unlikely to be a major factor because our gender specific prevalence ratio was similar to that reported by Kars et al (fivefold higher for women than men)[24]. The subcategorisation of cases depends on the algorithms employed, which may also introduce some error when identifying cause. For example some patients with mild hyperprolactinaemia who did not have an MRI may have had abnormalities such as small tumours or stalk effect that were missed. Such patients may have been miscategorised, but such patients were not treated with dopamine agonists or pituitary surgery, and it is unlikely that this was of clinical significance. Besides, we may have overestimated drug-induced hyperprolactinaemia, because if there was no other obvious cause for a raised serum prolactin (e.g. tumour or pregnancy), and a patient was on a drug that could cause hyperprolactinaemia, it was assumed to be the cause. Unfortunately we do not have data on whether serum prolactin concentrations decreased when/if the causative drug was withdrawn. The main impact of this would be an under diagnosis of "idiopathic" causes. It is difficult to know what caused hyperprolactinaemia in the idiopathic group but could have included "over the counter"

medications e.g. anti-emetics, or early pregnancy which subsequently ended in miscarriage and longstanding untreated pituitary micro-adenomas that were not identified on other datasets. Another possibility is that idiopathic hyperprolactinaemia was due to polycystic ovary syndrome, and indeed the peak incidence of idiopathic hyperprolactinaemia was in young women. Unfortunately our data linkage and algorithms do not allow us to identify this phenotype. Hypothyroidism as a cause of hyperprolactinaemia may be an overestimate as our threshold of serum TSH at 6mU/L (0.28ng/ml) is quite low, although other studies have shown a similar or higher prevalence of hyperprolactinaemia in series of patients with overt or subclinical hypothyroidism (8- 36%) [34, 35]. However, our study is genuinely population-based and will have identified all cases of raised prolactin concentrations that were measured in Tayside.

CONCLUSION

In summary, this study demonstrates that overall prevalence of ever diagnosed hyperprolactinaemia in Tayside, Scotland, is 0.1%. Incidence rates are five times higher in women than in men, but are approximately the same over the age of 65 years. The observed increasing rate over time is possibly due to increased ascertainment and to an increased use of psychotropic drugs.

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FIGURE LEGENDS

FIGURE 1. Incidence rates of hyperprolactinaemia by age and sex groups.

FIGURE 2. Age-sex specific incidence rates of hyperprolactinaemia by cause of hyperprolactinaemia.

TABLES

TABLE 1 Description at first event of diagnosis of case patients not associated to pregnancy in Tayside from 1988 to 2014 by cause of hyperprolactinaemia.

Characteristic	ALL	Pituitary disorder P *	Drug induced	Macroprolactin	Hypothyroidism	Idiopathic
n (%)	1,301 (100.0)	331 (25.4)	598 (45.9)	97 (7.5)	79 (6.1)	196 (15.0)
Gender (female)	1,019 (78.3)	258 (78.0)	467 (78.1)	76 (78.4)	59 (74.7)	159 (81.1)
Mean (SD)						
Age (years)	39.2 (16.4)	39.3 (16.3)	41.9 (16.1)	35.1 (14.1)	33.0 (20.5)	35.2 (14.9)
Prolactin (mU/L) †	1,636 (1,230-2,561)	2,426 (1,553- 5,310)	1,666 (1,266- 2,446)	1,321 (1,104- 1,899)	1,406 (1,157- 1,794)	1,298 (1,113- 1,755)

SD= standard deviation (*) Difference among subgroups (†) Maximum serum concentration: median (interquartile range). The conversion factor from units to mass be 21.2; (mU/L)/21.2= ng/ml

TABLE 2. Prevalence of hyperprolactinaemia per calendar year by sex (1993- 2013)

YEAR	WOMEN Cases/population	Prevalence per 100,000	MEN Cases/population	Prevalence per 100,000
	TOTAL Cases/population	Prevalence per 100,000		
1993	76/ 205,937	36.9	11/ 189,543	5.8
	87/ 395,480	21.9		
1994	93/ 205,913	45.1	14/ 190,067	7.3
	107/ 395,980	27.0		
1995	124/ 206,640	60.0	16/ 190,600	8.3
	140/ 397,240	35.2		
1996	154/ 206,023	74.7	21/ 189,877	11.0
	175/ 395,900	44.2		
1997	180/ 205,793	87.4	26/ 189,537	13.7
	206/ 395,330	52.1		
1998	206/ 205,053	100.4	27/ 188,997	14.2
	233/ 394,050	59.1		
1999	231/ 204,327	113.0	30/ 188,403	15.9
	261/ 392,730	66.4		
2000	255/ 203,098	125.5	35/ 187,332	18.6
	290/ 390,430	74.2		
2001	280/ 202,152	138.5	39/ 186,628	20.8
	319/ 388,780	82.0		
2002	310/ 201,947	153.5	45/ 186,363	24.1
	355/ 388,310	91.4		
2003	345/ 202,257	170.5	52/ 186,483	27.8
	397/ 388,740	102.1		
2004	367/ 202,971	180.8	56/ 187,199	29.9
	423/ 390,170	108.4		
2005	404/ 204,332	197.7	65/ 188,668	34.4
	469/ 393,000	119.3		
2006	445/ 205,421	216.6	71/ 189,839	37.4
	516/ 395,260	130.5		

2007	493/ 206,843	238.3		94/ 191,537	49.0
	587/ 398,380		147.3		
2008	553/ 208,410	265.3		110/ 193,500	56.8
	663/ 401,910		164.9		
2009	600/ 209,437	286.4		130/ 194,933	66.6
	730/ 404,370		180.5		
2010	650/ 210,510	308.7		148/ 196,560	75.2
	798/ 407,070		196.0		
2011	700/ 211,607	330.8		172/ 198,643	86.5
	872/ 410,250		212.5		
2012	767/ 212,161	361.5		188/ 199,589	94.1
	955/ 411,750		231.9		
Overall	--	**175.2**		--	**35.1**
	--		**107.3**		
[95%CI]		**[171.5- 179.6]**			**[33.5- 37.3]**
			[105.8- 110.5]		

TABLE 3. Incidence rate (per 100,000 person-years) of hyperprolactinaemia per year period by sex (1993- 2013)

		WOMEN		MEN	
		TOTAL			
PERIOD	Tests †	Crude Crude	Adjusted * Adjusted *	Crude	Adjusted *
1993- 1997	10,187	15.9 9.3	16.0 [13.5- 18.4] 9.2 [7.9- 10.6]	2.1	2.2
[1.2- 3.2]					
1998- 2002	9,167	16.8 11.0	17.0 [14.5- 19.6] 11.0 [9.5- 12.5]	4.7	4.9
[3.4- 6.3]					
2003- 2007	34,221	22.1 15.0	22.9 [19.9- 25.9] 15.2 [13.5- 17.0]	7.2	7.3
[5.6- 9.1]					
2008- 2013	42,487	28.6 20.1	29.8 [26.4- 33.2] 20.6 [18.6- 22.6]	11.0	11.1
[9.0- 13.2]					
Overall	**96,062**	**20.9** **13.8**	**21.5 [20.0- 22.9]** **13.8 [13.1- 14.7]**	**6.3**	**6.4**
[5.6- 7.2]					

(*) Age-sex standardized [95% Confidence interval]

(†) Number of prolactin tests performed in Tayside.

TABLE 4. Incidence rate (per 100,000 person-years) of hyperprolactinaemia per year period by sex and cause (1993- 2013)

PERIOD	WOMEN		TOTAL	MEN	
	Crude	Adjusted *	Adjusted *	Crude	Adjusted *
PITUITARY DISORDER					
1993- 1997	4.7	2.9 [2.1- 3.6]	4.7 [3.4- 6.1]	0.9	1.0 [0.3- 1.7]
1998- 2002	5.8	3.9 [3.0- 4.7]	5.8 [4.4- 7.3]	1.8	1.9 [1.0- 2.8]
2003- 2007	6.9	4.1 [3.2- 5.0]	7.1 [5.4- 8.7]	1.1	1.1 [0.4- 1.7]
2008- 2013	4.6	3.7 [2.9- 4.5]	4.7 [3.4- 6.1]	2.6	2.7 [1.6- 3.7]
Overall	**5.5**	**3.6 [3.2- 4.1]**	**5.6 [4.9- 6.3]**	**1.6**	**1.7 [1.3- 2.1]**
DRUG INDUCED					
1993- 1997	5.7	3.2 [2.4- 4.0]	5.7 [4.3- 7.2]	0.5	0.6 [0.1- 1.1]
1998- 2002	5.7	3.6 [2.7- 4.4]	5.8 [4.3- 7.3]	1.3	1.4 [0.6- 2.1]
2003- 2007	11.1	7.8 [6.6- 9.1]	11.3 [9.2- 13.4]	4.1	4.2 [2.9- 5.5]
2008- 2013	16.7	11.8 [10.3- 13.3]	17.3 [14.7- 19.9]	6.0	6.1 [4.5- 7.6]
Overall	**9.9**	**6.7 [6.1- 7.2]**	**10.1 [9.1- 11.1]**	**3.0**	**3.1 [2.5- 3.7]**
MACROPROLACTIN					
1993- 1997	0.1	0.1 [0.0- 0.3]	0.1 [0.0- 0.3]	0.1	0.1 [0.0- 0.4]
1998- 2002	0.2	0.1 [0.0- 0.3]	0.2 [0.0- 0.5]	0.0	-
2003- 2007	0.8	0.7 [0.3- 1.1]	0.8 [0.3- 1.4]	0.5	0.5 [0.1- 1.0]

2008- 2013			4.7	4.9 3.6- 6.3]	1.4	1.4
[0.7- 2.2]	3.1		3.2 [2.4- 4.0]			
Overall			**1.5**	**1.5 [1.1- 1.9]**	**0.5**	**0.5**
[0.3- 0.7]	**1.0**		**1.0 [0.8- 1.2]**			
HYPOTHYROIDISM						
1993- 1997			2.0	2.1 [1.2- 2.9]	0.5	0.5
[0.1- 0.9]	1.3		1.3 [0.8- 1.8]			
1998- 2002			0.7	0.7 [0.2- 1.3]	0.3	0.4
[0.0- 0.8]	0.5		0.5 [0.2- 0.9]			
2003- 2007			0.8	0.8 [0.2- 1.3]	0.5	0.5
[0.1- 1.0]	0.7		0.6 [0.3- 1.0]			
2008- 2013			0.8	0.8 [0.2- 1.3]	0.3	0.3
[0.0- 0.6]	0.5		0.5 [0.2- 0.9]			
Overall			**1.1**	**1.1 0.8- 1.4]**	**0.4**	**0.4**
[0.2- 0.6]	**0.8**		**0.8 [0.6- 1.0]**			
IDIOPATHIC						
1993- 1997			3.4	3.3 [2.2- 4.5]	0.0	-
		1.8		1.7 [1.1- 2.3]		
1998- 2002			4.4	4.5 [3.2- 5.8]	1.3	1.3
[0.6- 2.0]	2.9		2.9 [2.2- 3.7]			
2003- 2007			2.6	2.9 [1.8- 3.9]	1.0	1.0
[0.3- 1.6]	1.8		1.9 [1.3- 2.5]			
2008- 2013			1.9	2.0 [1.1- 2.9]	0.6	0.6
[0.1- 1.2]	1.3		1.3 [0.8- 1.9]			
Overall			**3.1**	**3.2 [2.6- 3.7]**	**0.7**	**0.7**
[0.4- 1.0]	**1.9**		**2.0 [1.7- 2.3]**			

(*) Age-sex standardized [95% Confidence interval]